
Embryonic stem cell self-renewal pathways converge on the transcription factor Tfcp2l1.

Journal:	EMBO J
Publication Year:	2013
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PubMed link:	23942238
Funding Grants:	Self-renewal of human embryonic stem cells, Mechanisms Underlying the Diverse Functions of STAT3 in Embryonic Stem Cell Fate Regulation, CIRM Stem Cell Biology Training Program

Public Summary:

Embryonic stem cells can self-renew in culture indefinitely while retaining the ability to differentiate into any type of cell in the body. How embryonic stem cell self-renewal is maintained, however, is still poorly understood. Here, we revealed the important role of Tfcp2l1 in maintaining embryonic stem cell self-renewal. Tfcp2l1 is a transcription factor, or protein that controls which genes are turned on and off in a cell. Increased expression of Tfcp2l1 keeps mouse embryonic stem cells in an undifferentiated state. Tfcp2l1 also shows promise for "rewinding" slightly more differentiated epiblast stem cells into the more naïve embryonic stem cell state. Our study will allow us to better control stem cell self-renewal, offering hope for patients with currently untreatable diseases and creating potential for a wide variety of other applications.

Scientific Abstract:

Mouse embryonic stem cell (mESC) self-renewal can be maintained by activation of the leukaemia inhibitory factor (LIF)/signal transducer and activator of transcription 3 (Stat3) signalling pathway or dual inhibition (2i) of glycogen synthase kinase 3 (Gsk3) and mitogen-activated protein kinase kinase (MEK). Several downstream targets of the pathways involved have been identified that when individually overexpressed can partially support self-renewal. However, none of these targets is shared among the involved pathways. Here, we show that the CP2 family transcription factor Tfcp2l1 is a common target in LIF/Stat3- and 2i-mediated self-renewal, and forced expression of Tfcp2l1 can recapitulate the self-renewal-promoting effect of LIF or either of the 2i components. In addition, Tfcp2l1 can reprogram post-implantation epiblast stem cells to naïve pluripotent ESCs. Tfcp2l1 upregulates Nanog expression and promotes self-renewal in a Nanog-dependent manner. We conclude that Tfcp2l1 is at the intersection of LIF- and 2i-mediated self-renewal pathways and plays a critical role in maintaining ESC identity. Our study provides an expanded understanding of the current model of ground-state pluripotency.

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